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Inquiry-Based Learning: Inflammation as a Model to Teach Molecular Techniques for Assessing Gene Expression †

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This laboratory module simulates the process used by working scientists to ask and answer a question of biological interest. Instructors facilitate acquisition of knowledge using a comprehensive, inquiry-based approach in which students learn theory, hypothesis development, experimental design, and data interpretation and presentation. Using inflammation in macrophages as a model system, students perform a series of molecular biology techniques to address the biological question: "Does stimulus 'X' induce inflammation?" To ask this question, macrophage cells are treated with putative inflammatory mediators and then assayed for evidence of inflammatory response. Students become familiar with their assigned mediator and the relationship between their mediator and inflammation by conducting literature searches, then using this information to generate hypotheses which address the effect of their mediator on induction of inflammation. The cellular and molecular approaches used to test their hypotheses include transfection and luciferase reporter assay, immunoblot, fluorescence microscopy, enzyme-linked immunosorbent assay, and quantitative PCR. Quantitative and qualitative reasoning skills are developed through data analysis and demonstrated by successful completion of post-lab worksheets and the generation and oral presentation of a scientific poster. Learning objective assessment relies on four instruments: pre-lab quizzes, post-lab worksheets, poster presentation, and posttest. Within three cohorts (n = 85) more than 95% of our students successfully achieved the learning objectives.

INTRODUCTION

Inquiry-based laboratory experiences that facilitate learning techniques in the larger context of an experimental question are more effective in increasing student understanding (2). In essence, inquiry-based teaching represents a form of cognitive apprenticeship (CA), a theory that asserts students learn most naturally in an environment where skills are developed by creating an authentic context for student learning (4). It is modeled on the traditional master-apprentice system of aquiring knowledge; as a learning model, CA represents an instructional paradigm that adapts the master-apprentice relationship to suit learning in other intellectual disciplines (3). Since its original description, CA has been used effectively in a number of disciplines including the natural sciences; essentially it represents a constructivist, inquiry-based approach in which the instructor guides the students through the process of knowledge acquisition by modeling, coaching, and then stepping back to allow the student the opportunity to address the problem with greater independence (4, 5–7).

To approach the goal of developing an inquiry-based laboratory curriculum, we have developed a laboratory module that utilizes inflammation in macrophages to teach the molecular approaches scientists use to assess gene expression events. This module allows students to address a central question regarding inflammation using a number of molecular techniques including transfection, luciferase assay, immunoblot analysis (western blot), enzyme-linked immunosorbent assay (ELISA), fluorescence microscopy, and quantitative real time polymerase chain reaction (qPCR). Students are able to use knowledge gained in the module along with their experimental results to form a comprehensive answer to the question, "Does treatment "X" induce inflammation?" By approaching the same question from multiple aspects, the students are able to develop a more complete understanding of the mechanisms that account for their observations. This laboratory module uses Level 2, structured inquiry-based learning to simulate the process a scientist uses to move a hypothesis from conception to testing (1). The module provides students with a research question and prescribed procedures; students research the topic, conduct experiments, interpret data, and make conclusions. Upon module completion students cite data to support their conclusions, thereby demonstrating the connection between the techniques and the scientific process.

The student cohorts for this curriculum represent high school students, most of whom are rising seniors that have

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participated in a one-year-long, advanced course in molecular genetics. Students earning C or above in their high school molecular genetics course are eligible to participate in our biotechnology course module. Upon successful completion of the module (C or above) students earn four college science credits. Thus, our program provides a capstone experience to their high school molecular genetics course and extends the experimental methodologies to which students are exposed.

Historically, our summer laboratory experience was strictly a lab techniques course aimed at exposing students to methods with very little focus on hypothesis development or data analysis. In an effort to improve the course and test the utility of our inquiry-based approach, we have redesigned it to follow the curriculum outlined here. In the current, inquiry-based version, students spend two weeks on our campus and complete an *undergraduate-level* course in biotechnology and molecular biology. Students work together in groups of two to three; each group is assigned a particular inflammatory mediator or combination of mediators. Mediators may include lipopolysaccharide (LPS), interferon-gamma (IFN-γ), phytohemagglutinin (PHA), phorbol 12-myristate 13-acetate (PMA), and homocysteine. To aid in their understanding of the model system, each group conducts a literature review of inflammation and their specific mediator. They then develop a hypothesis to address whether the mediator will induce inflammation. As the module progresses, students generate hypotheses for each technique and experiment performed. Five different experiments are conducted, each emphasizing a different technique and facet of the inflammatory response. Using sterile technique and tissue culture, groups treat the murine macrophage cell line RAW264.7 with their designated mediator. For some experiments, cells are transfected prior to treatment. Following treatment, students analyze cells for induction of inflammation as measured by: NFκB promoter activity (luciferase assay); NFκB protein expression and localization (immunoblot and fluorescence microscopy); TNFα protein production (ELISA); and mRNA expression of iNOS, NFκB, and TNFα (qPCR).

Intended audience

This laboratory module is targeted to students who have had exposure to genetics and molecular techniques at the introductory undergraduate level. While our cohort of students for this study was upper-level high school students, prior to participation these students have completed a year-long course in prokaryotic molecular genetics at their high school that is the equivalent of an advanced placement course. Thus, students entering our course possess fundamental knowledge of molecular genetics equivalent to an undergraduate who has completed first year. Given that our students are advanced high school students, this module could be easily adapted to an undergraduate biology course that emphasizes cellular and molecular biology techniques. In fact, at our institution, individual exercises from the module are employed across various courses including immunology, molecular biology, and genetics. Alternatively, the entire module could be used as the laboratory experience for a single semester-long course.

Learning time

Our two-week module is taught as an intensive course conducted over nine days, with students spending eight days (six hours/day) in the laboratory. Laboratory days are broken up into lecture, laboratory, data analysis, and poster preparation time. The final day is used for data presentation in the form of a two-hour, public poster session during which students orally and visually present their findings (Table 1). Refer to the 'Possible Modifications' section for alternative time management options.

Prerequisite knowledge and safety considerations

Participating students must possess undergraduate introductory-level biology knowledge along with a basic understanding of the central dogma of molecular biology and gene expression at the transcriptional and translational levels. Students do not possess a background in inflammation; conceptual information about inflammation and the procedures used to test inflammation are taught as needed during short pre-lab lectures. In addition, students have had limited exposure to the techniques used. Therefore, discussion of the theory behind each technique is also provided.

In addition to conceptual knowledge, students arrive having been exposed to basic laboratory safety protocols and are familiar with the use of micropipettes. Typically, upper level undergraduate students serve as teaching assistants. Prior to the course, instructors meet with the teaching assistants to review proper safety procedures both for themselves and in the event that student safety is jeopardized. Students are made aware of safety considerations and available safety equipment throughout the duration of the course. Food and drink are prohibited in the lab and a laboratory dress code is enforced. Buffers used in most experiments can irritate skin, and reagents used in fluorescence microscopy and qPCR can be mutagenic. To alleviate safety concerns, we utilize pre-poured polyacryalmide gels and require that students wear gloves during all lab activities. Lab coats are provided.

Learning objectives

The course was designed with the following five learning objectives in mind (see Appendix 1 for assessment information):

1. Students will demonstrate understanding of the theory, practice, and experimental design for the specific cellular and molecular laboratory techniques they use through both written and oral communication.

TABLE 1.
Student performance on quizzes, post-lab questions, and posters.[a]

Student	Quiz 1 (10)	Quiz 2 (10)	Quiz 3 (10)	Quiz 4 (10)	Quiz 5 (10)	Post-Lab 1 (10)	Post-Lab 2 (10)	Post-Lab 3 (20)	Post-Lab 4 (10)	Poster (100)	%/Grade
#1	10	9	10	10	8	10	7	18.5	9.5	98	95/A
#2	10	9	10	9	8	9.5	7.5	18	10	97.5	94/A
#3	10	9	9	10	10	9	8.5	19.5	9.5	97.5	96/A
#4	10	10	8	10	9	7.5	7	16.5	9.5	82	85/B
#5	10	9	8	8	6	10	7.5	19.5	10	93.5	91/A-
#6	10	9	5	8	7	10	8.5	17	9.5	83.5	84/B
#7	10	9	9	9	9	9.5	8.5	17	9.5	93.5	92/A-
#8	10	9	9	9	9	9	9	18	9	82	87/B+
#9	10	9	7	9	7	10	9	18.5	10	82	86/B+
#10	10	9	10	9	8	8.5	7	18.5	8	97.5	93/A
#11	10	8	8	10	9	8	8	18.5	10	98	94/A
#12	10	10	6	9	9	10	8	19.5	10	98	95/A
#13	10	9	9	8	8	10	9	17.5	10	98	94/A
#14	10	8	7	7	8	8.5	9.5	17	8	88	86/B
#15	10	10	9	8	9	7	8	18.5	7.5	87	87/B+
#16	10	10	9	8	9	9	9.5	17.5	9	88	90/A-
#17	10	8	8	9	6	10	8	17.5	9	98	92/A-
#18	10	10	9	7	9	8.5	9	16.5	9	87	88/B+
#19	10	9	6	9	5	10	8.5	18.5	9	87	86/B
#20	10	9	9	9	9	9.5	9	19.5	10	98	96/A
#21	10	10	10	10	9	8.5	8.5	19	10	88	92/A-
Average	10.0	9.1	8.3	8.8	8.1	9.1	8.3	18.1	9.3	91.5	90.4/A

[a]Individual scores and averages awarded for each graded assignment and overall grade earned are indicated for each student (n = 21). Maximum possible points for each assignment are in parentheses.

2. Students will conduct a review of the primary literature and demonstrate understanding of the process of inflammation and the role of their mediator through written and oral communication in the poster presentation.
3. Students will demonstrate the ability to develop hypotheses and predict experimental outcomes through oral communication and written responses to guided questions.
4. Students will summarize their experience and demonstrate the knowledge they have gained through oral, visual, and written communication.
5. Students will gain direct experience with molecular laboratory techniques and demonstrate: 1) comprehension of functionality and usefulness; 2) appropriate data presentation format; and 3) data interpretation for each method used through written response and oral presentation.

PROCEDURE

Materials and student instructions

Reagent and equipment requirements are described in Appendix 2. Students are provided with a laboratory manual that provides background information and experimental protocols (Appendix 3).

Faculty instructions

Pre-laboratory lecture topics. Students lack familiarity with inflammatory processes and molecules and the molecular techniques used. Thus, pre-laboratory lecture time should be dedicated to exploring inflammation as a model system, key inflammatory molecules (TNFα, NFκB, and gene targets), and the molecular theory behind the laboratory techniques. Review articles on inflammatory

processes and molecules are provided in addition to the laboratory manual (see Appendix 4, reference list).

Implementation. The experimental timeline is provided in Figure 1. Teaching notes including a timeline for dissemination of conceptual information, pre-lab lectures, quizzes, pre-lab reading, and steps that, in the interest of time, need to be completed by lab aides are provided in Appendix 4. Samples quizzes, post-laboratory worksheets, and answer keys can be found in Appendix 6. Instructors should make efforts to help students draw the connections among the various techniques such that they gain an understanding of what it means to answer a biological question in a comprehensive way. To do this, our instructors emphasize three points: 1) functionality and usefulness of assays, 2) data formatting and presentation, and 3) data interpretation. These three areas serve as the foundation of the assessment tool used in this study (Appendix 5).

Determining student learning outcomes

Course grades are determined as follows: pre-lab quizzes (25%), written post-lab worksheet responses (25%), and generation and oral presentation of a scientific poster (50%). Successful completion of these assignments serves as an indicator of learning. Multiple-choice pre-lab quizzes are intended to motivate students to prepare for lecture; whether they are a good indicator of learning likely depends on the cohort in question; our 2012 cohort performed quite well on the quizzes (Table 1). On the final day of the course, students present their findings in a public poster presentation. Posters are judged by multiple faculty using a common rubric (Appendix 3).

Upon completion of the entire module, students provide written responses to an assessment tool (AT) developed for this course module. The AT serves as our most objective assessment method. Since this assessment takes place at the end of the module, it is a good indicator of comprehensive learning and measures students' ability to think about the different techniques learned, in relation to one another, rather than one at a time as in the post-lab worksheets. Because our student cohorts enter with little exposure to the techniques used, we do not administer the AT as a pretest. However, the AT does provide the opportunity for students to state whether they had the ability to answer any of the questions prior to taking the

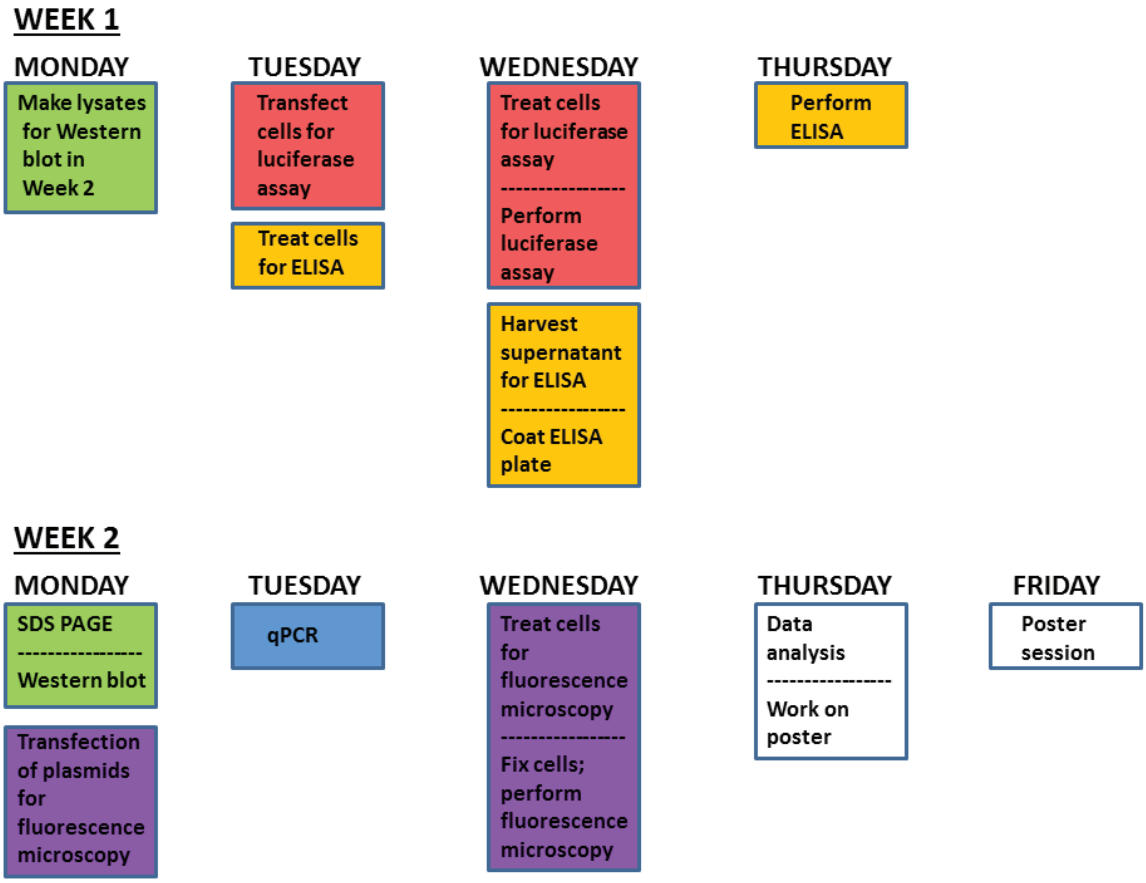

FIGURE 1. Experimental daily work chart for the MASE (Mount Academy for Scientific Excellence) program. Experiments are color-coded to show experimental progression across multiple days. Red boxes: luciferase assay; orange boxes: ELISA; green boxes: western blot; blue box: qPCR; purple boxes: fluorescence microscopy. White boxes show time reserved for data analysis, work on the poster, and the poster presentation.

course. When using this tool with undergraduate student populations, we recommend the AT be given both as a pretest and posttest.

To evaluate instructor effectiveness and overall student perception of the course, students complete a course evaluation (Appendix 7).

Sample data

Examples of data generated by student groups using LPS as a mediator are shown in Figures 2–4. Students hypothesized that LPS would induce inflammation, including activation of the NFκB promoter, production of TNFα, and increased mRNA expression of iNOS, TNFα, and NFκB. Additional results from our 2011 and 2012 cohorts are summarized in Appendix 8.

DISCUSSION

Field testing and evidence of student learning

This curriculum has been used in its current form since 2010. qPCR was added in 2012. Since 2010, 85 students have enrolled in the course; only two have earned below a C- and did not earn college credit. Grading criteria for past cohorts has been similar; however 2012 represents the first year for pre-lab quizzes, post-lab worksheets, and the AT. Final grades for past cohorts also included performance on pre-lab worksheets and lab notebooks. Between 2011 and 2012, we streamlined the grading process and identified methods to better prepare students for the poster session. Lab notebooks were replaced by post-lab worksheets to guide students through presentation of results and analysis of data; our experience suggested that having students construct written responses to guided questions after the laboratory provided better understanding of the laboratory procedures than notebook keeping. We also replaced written answers to pre-lab questions with pre-lab multiple-choice quizzes. In the past, questions were graded for completion rather than correctness and did not serve as a reliable indicator of student preparation. Replacement with quizzes allowed us to simultaneously motivate students to prepare for lab and to assess student preparation.

Quiz, post-lab worksheet, poster presentation, and overall performance data for each student in the 2012 cohort are provided (Table 1) and allow assessment of each of the five learning objectives. One hundred percent were successful in achieving the learning objectives, earning a B or higher in the course and college credit.

Implementation of the AT in 2012 allowed us to assess the learning objectives via an additional mechanism (n = 21). Tables 2–4 show the AT questions. Part 1 deals with functionality and usefulness of techniques (Table 2), while Part 2 focuses on data presentation format for each technique (Table 3). Part 3 assesses student ability to interpret data (Table 4 and Appendix 9).

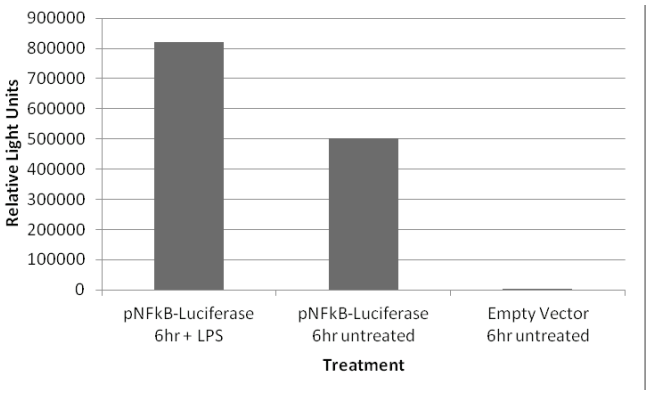

FIGURE 2. Student-generated data: effect of LPS on NFκB promoter activity, by luciferase reporter assay.

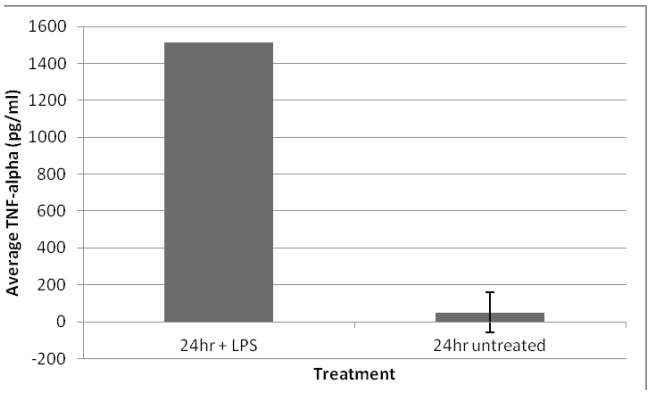

FIGURE 3. Student-generated data: effect of LPS on TNFα secretion, by ELISA. n = 3, error bars represent standard deviation.

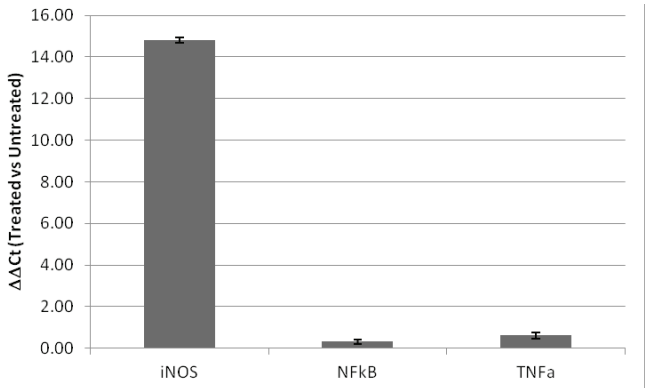

FIGURE 4. Student-generated data: effect of LPS on mRNA expression of iNOS, NFκB, and TNFα, using qPCR. Error bars indicate standard deviation; n = 3.

Assessment questions 8 and 13 allow students to comment on knowledge they possessed prior to the course; seven students had heard of one or more techniques, but none could interpret the data before taking the course. Following the course, the vast majority of students understand which techniques utilize enzymes and antibodies, and they can also state what the technique directly assays (Table 3). Luciferase assay and qPCR were the most difficult topics for the students. Regarding ability to match the method with

TABLE 2.
Part 1 of the assessment tool.

Part 1: Questions 1–6 asked multiple-choice style questions where students were asked to circle all correct responses. Shown below are the correct answers and the percentage of students who selected that correct response.
Q1: Which techniques utilize antibodies? –ELISA (100%) –Western blot (42.9%)
Q2: Which techniques are used to detect either the presence of a protein or the activity of a protein? –Luciferase assay (57.1%) –Western blot (95.2%) –Fluorescence microscopy (71.4%)
Q3: Which techniques are used to analyze transcription but not translation? –qPCR (71.4%)
Q4: Which techniques utilize an enzyme? –Luciferase assay (90.5%) –ELISA (100%) –Western blot (23.8%) –qPCR (33.3%)
Q5: Which techniques can provide information about the specific location (compartment/organelle) of a protein inside of a cell? –Western blot (85.7%) –Fluorescence microscopy (100%)
Q6: Define transfection, and state the value of transfection in one of the experiments you conducted during MASE (Mount Academy for Scientific Excellence). –In this free response, we graded 95.2% to have properly defined transfection and 76.2% to have accurately applied the value of transfection experimentally.
Q7: Retrospective question: Prior to MASE, did you possess the knowledge to correctly answer any of the above questions (1–6)? If yes, please state which ones. –Of the 21 students, only 3 reported familiarity with western blotting and thought that they could have identified the correct responses in the questions related to western blots.

TABLE 3.
Part 2 of the assessment tool.

Part 2: In questions 8–12, students were shown sample data and asked which technique would have been utilized to generate the data shown. Each of the 6 questions is shown along with the correct response and the percentage of students who selected the correct response.
Q8: Sample luciferase assay data (100% of students correctly identified this as luciferase assay data)
Q9: Sample qPCR data (100% of students correctly identified this as qPCR data)
Q10: Sample ELISA data (90.5% of students correctly identified this as ELISA data)
Q11: Sample fluorescence microscopy data (100% of students correctly identified this as fluorescence microscopy data)
Q12: Sample Western blot data (100% of students correctly identified this as Western blot data)
Q13: Retrospective question: Prior to MASE, did you possess the knowledge to correctly answer any of the above questions (8–12)? If yes, please state which ones? –Of the 21 students, 6 reported familiarity with some of the techniques, but stated that while they might have been able to recognize sample data, they would not have been able to analyze the data.

the formatted data, 19 of 21 students responded correctly to all questions (Table 3).

Analysis of the Part 3 (Q14–18) data indicates that, overall, students were able to interpret hypothetical data presented in a format similar to that which they used for their posters (Table 4). Students struggled with luciferase assay data and fluorescence microscopy data. In the AT, the fluorescence microscopy data the students were presented with showed translocation of a protein out of the nucleus rather than into the nucleus; this was the opposite of what students expected to see in their own experiments. This increased the rigor of the question; the widespread inability of the students to correctly answer the question demonstrated that full comprehension and interpretive maturity are lacking; we feel this is understandable given the introductory level of these students.

Taken together, analysis of the AT responses shows that students struggled most with correctly interpreting luciferase assay, fluorescence microscopy, and qPCR data. As mentioned, the difficulty with fluorescence microscopy data may be accounted for in the design of the assessment question. Questions showing luciferase assay and qPCR data were presented in a similar fashion to what students had been shown during the course. The root of the incorrect luciferase assay data interpretation is articulation of what the assay actually shows rather than what the data imply. Deficiencies in comprehension may reflect the increased complexity of these assays relative to the students' level of experience and maturity. Additionally, it suggests that more time should be dedicated to discussion of the theory of these techniques. A summary of student responses to AT Part 3 is provided (Appendix 9).

In any laboratory endeavor, experiments sometimes do not work as anticipated. Our course module is no exception. Individual groups occasionally obtain unexpected results or no results due to errors in setup or execution of a particular assay. In these cases, instructors address troubleshooting with the students by discussing how to think through the possible reasons to account for the

TABLE 4.
Part 3 of the assessment tool.

Part 3: Questions 14–18 involved data interpretation. Students were presented with sample data and had to apply their knowledge to make conclusions regarding sample experimental results. Each of the 5 questions is summarized along with the percentage of students who generated an appropriate response.

Q14: qPCR: According to the data, which gene demonstrates the greatest change in expression between treated and untreated conditions? In your answer, please refer to specific data from the table.

–85.7% of students gave correct responses

–14.3% of students gave partially correct responses

–0% of students gave incorrect responses

Q15: ELISA: According to the data, what is the effect of the mediator? In your answer, please refer to specific data from the figure.

–90.5% of students gave correct responses

–9.5% of students gave partially correct responses

–0% of students gave incorrect responses

Q16: Luciferase assay: According to the data, what is the effect of the mediator? In your answer, please refer to specific data from the figure.

–76.2% of students gave correct responses

–19.1% of students gave partially correct responses

–4.7% of students gave incorrect responses

Q17: Western blot analysis: According to the data, what is the overall effect of the mediator? In your answer, please refer to specific data from the figure.

–85.7% of students gave correct responses

–0% of students gave partially correct responses

–14.3% of students gave incorrect responses

Q18: Fluorescence microscopy: According to the data, what is the effect of the mediator after 2 hours of treatment? In your answer, please refer to specific data from the figure.

–38.1% of students gave correct responses

–42.9% of students gave partially correct responses

–19% of students gave incorrect responses

unexpected results. In this way, the instructors model for students the thought process working scientists use to address experimental challenges.

After completion of the experiments, data analysis, and poster generation, students evaluated the course on a scale from 1 to 5 (1 – unsatisfactory, 2 – poor, 3 – satisfactory, 4 – very good, 5 – excellent). Students also commented on the difficulty of the course on a scale from 1 to 5 (1 – too easy, 3 – just right, 5 – too hard) (Fig. 5). Written comments revealed that the students enjoyed the experience and felt they learned interesting new material. Several students commented they would like more time to work on their posters; while our timeline does not allow

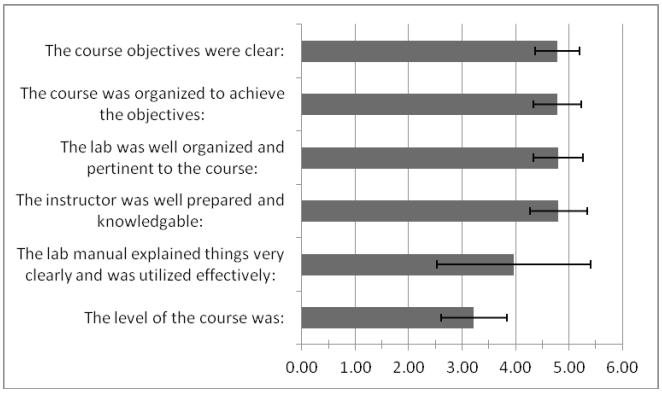

FIGURE 5. Student evaluation of the module. Bars represent the mean and standard error of the mean, n = 21. (1 – unsatisfactory, 2 – poor, 3 – satisfactory, 4 – very good, 5 – excellent). For level of course (1 – too easy, 3 – just right, 5 – too hard).

for that, more time could be devoted to poster preparation if the curriculum was spread over a semester rather than over two weeks.

Overall, our analysis indicates increased student knowledge of eukaryotic gene expression and facility with molecular biology methods through completion of this module. Our results indicate that this curriculum met all of the stated objectives.

Possible modifications

Alternative delivery strategies include adjusting the laboratory module to fit a typical semester-long schedule or using selected experiments from the module rather than the whole. A modified semester-long approach would work well for a biotechnology methods class or immunology course wishing to use inflammation as an experimental model. It would also fit well into a molecular and cellular biology course where emphasis could be placed on cellular gene expression.

Currently, our institution uses selected experiments from the module in various courses. qPCR analysis is conducted in our introductory genetics course. The luciferase assay and fluorescence microscopy experiments are used in our molecular and cellular biology course. Immunology students utilize the ELISA to learn the concept of the ELISA and to reinforce macrophage innate immune responses. As an extension, immunology students analyze macrophage nitric oxide production and costimulatory molecule upregulation in response to the same mediators used in the ELISA analysis.

In our course module, student groups report the findings of their individual group. However, in upper-level undergraduate or capstone courses, it might be desirable to have students analyze all class data and report on combined and synthesized findings rather than solely their own mediator. Additionally, students could be allowed to choose their own stimuli thereby moving this to a Level 3 inquiry-based learning approach.

SUPPLEMENTAL MATERIALS

Appendix 1: Assessment of learning objectives
Appendix 2: Materials, instrumentation, orders, and recipes
Appendix 3: MASE Biotechnology Camp Lab Manual
Appendix 4: Teaching notes (including daily flow and review reference list)
Appendix 5: MASE Assessment Tool (MAT)
Appendix 6: Quizzes and post-lab worksheets
Appendix 7: Student evaluation of MASE
Appendix 8: Results from 2011 and 2012 cohorts
Appendix 9: Assessment tool data part 3
Appendix 10: Spreadsheets for qPCR and ELISA data analysis

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